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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,728	07/03/2003	Jeffrey Robbins	CHM02-GN053	8201

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,728	ROBBINS, JEFFREY	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *16-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/6/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-15 in the reply filed on 6/07/2005 is acknowledged.

2. Claims 16-37 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed 6/07/2005.

3. Claims 1-15 drawn to an isolated nucleic acid having the nucleotide sequence comprising the sequence set for in SEQ ID NO:1, an expression cassette, vector and host cell comprising the isolated nucleic acid of SEQ ID NO: 1, an isolated nucleic acid molecule having a nucleotide sequence having at least 95% identity to the sequence set forth in SEQ ID NO: 1, wherein said nucleotide sequence is capable of initiating transcription in cardiac tissue, and an expression cassette, vector and host cell comprising an isolated nucleic acid molecule having a nucleotide sequence having at least 95% identity to the sequence set forth in SEQ ID NO: 1 is under consideration.

Objections

The specification discloses that the plasmids comprising SEQ ID NO: 1 of the invention were deposited with the Patent Depository of the American Type Culture Collection (pg. 8 parag. 3). However, the information pertaining to the deposit has been left blank. Applicant is advised to correct this omission with the corresponding information.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-5, and 12-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated host cells stably transformed with an expression cassette comprising an isolated nucleotide sequence set forth in SEQ ID NO: 1 operably linked to a nucleotide sequence of interest, does not reasonably provide enablement for any host cells stably transformed with an expression cassette comprising an isolated nucleotide sequence set forth in SEQ ID NO: 1 operably linked to a nucleotide sequence of interest. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not

disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a somatic cell that has been transformed *in vivo* or *in vitro* with the claimed expression cassettes. This embodiment reads on gene therapy.

Whereas the nature of the invention is a host cell comprising an isolated nucleic acid molecule that promotes cardiac-specific expression of a transgene of interest in an animal, a review of the current art teaches that the field of gene therapy is unpredictable. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three reviews. Concalves (2005, BioEssays, Vol. 27, pgs. 506-517) teaches that with respect to gene therapy "one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact of innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (pg. 514 col. 2 parag. 3). Specifically, Concalves teaches that gene therapy utilizing viruses has resulted in significant unpredictability, with retroviruses (pg. 513 col. 1 parag. 3 bridge col. 2 parag. 1), and adenoviruses (pg. 513, col. 2 parag. 2) providing only a fleeting success that was ultimately undone by a lack of transduction and low transgene expression levels. Parekh-Olmedo et al. teach (2005, Gene Therapy, Vol. 12, pgs. 639-646) with regard to gene repair utilizing gene therapy comprising single-stranded DNA oligonucleotides, repair of a gene of interest is again unpredictable. Specifically, successful gene repair has been reported in an animal model of

severe kidney disease comprising carbonic anhydrase-deficiency utilizing a single-stranded DNA vector (pg. 641 col. 1 parag. 3). However, in a LacZ mouse model designed for testing gene repair using a variety of vectors, no correction of the mutant LacZ gene was observed, resulting in the observation that delivery of DNA to a particular tissue continues to be a problem (pg. 641 col. 2 parag. 1). Verma et al. (2005, Annu. Rev. Biochem. Vol. 74, pgs. 711-738) teach that "the young field of gene therapy promises major medical progress toward a cure of a broad spectrum of human diseases from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but it has yet to deliver its promised potential" (pg. 732, parag, 2 lines 2-6). Verma et al. continues to teach that the process of gene delivery and expression is known as transduction, and that successful transduction requires overcoming a number of obstacles that are common to all vector systems (pg. 712, parag. 2 lines 1-3). Specifically, these obstacles include production of the vector, the targeting of the vector to a specified cell type, sustained gene expression, and avoidance of potential hazards such as insertional mutagenesis and immune responses (pg. 712, parag. 2 lines 3-19).

In view of the unpredictability of the art of gene therapy, a skilled artisan would require specific guidance in the instant disclosure to make and use the full scope of the claimed embodiment. Wherein the instant specification provides specific guidelines for transforming an isolated somatic cell *in vitro*, the instant specification however, has not provided any relevant teachings, guidance, or working examples that teach or otherwise correlate to transformation of a cell *in vivo* with one of the claimed expression vectors that would lead to expression of a transgene of interest. The specification has failed to provide any guidance or working examples that correlate administration of said expression vectors into a host with targeting of a particular

cell or tissue. One of normal skill in the art would not be able to rely on the state of the art of *in vivo* gene therapy to transform a somatic cell *in vivo* with an expression vector(s). Thus in view of the lack of guidance and direction provided by the specification for gene therapy of any cell in any animal, it would have required one of skill in the ad undue experimentation to make and use the invention as claimed.

The working examples provided in the instant specification teaches the steps to transform isolated single cell embryos of FVB/N mice with an expression vector comprising the ELC1a gene driven by the $MHCmin^{TetO}$ (SEQ ID NO: 1) (pg. 44 parag. 1). Therefore, in view of the lack of specific guidance and the unpredictability of the art of gene therapy as discussed above, a skilled artisan is not enabled for the full breadth of the claimed invention. Therefore, in view of the lack of direction or guidance provided by the instant specification for gene therapy using the claimed expression vectors and host cells, the quantity of experimentation necessary to determine the parameters listed above for producing a somatic cell transformed *in vivo* with the claimed expression vectors, the absence of working examples the demonstrate or otherwise correlate to transformation of a somatic cell *in vivo* with effective expression of the claimed expression vectors, and the unpredictability of the art of gene therapy with respect to obtaining any effect on any symptom of any disease or condition, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to isolated host cells stably

transformed with an expression cassette comprising an isolated nucleotide sequence set forth in SEQ ID NO: 1 operably linked to a nucleotide sequence of interest is proper.

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 9-15 are directed to an isolated nucleic acid molecule having a nucleotide sequence having at least 95% identity to the sequence set forth in SEQ ID NO:1, wherein said nucleotide sequence is capable of initiating transcription in cardiac tissue, an expression cassette comprising said isolated nucleic acid molecule operably linked to a nucleotide sequence of interest, a vector comprising said expression cassette, a host cell stably transformed with said expression cassette, wherein said host cell is an animal cell, wherein said isolated nucleic acid has ventricle preferred transcription, wherein said isolated nucleic acid has inducible transcription.

When the claims are analyzed in light of the specification, the instant invention encompasses any 95% of nucleotides in SEQ ID NO: 1 that will initiate transcription in cardiac tissue. However, the specification teaches only the full length nucleotide sequence of SEQ ID NO: 1. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the promoter of SEQ ID NO: 1 is the only species whose complete structure is disclosed. The specification does not provide any disclosure as to what the

structure would be of a nucleotide sequence having at least 95% identity to SEQ ID NO:1, wherein said nucleotide sequence is capable of initiating transcription in cardiac tissue. The specification teaches that the modified mouse alpha myosin heavy chain (MHC) promoter described in Transgenic Research (1995) 4: 397-405 was used as the starting point for making the minimal promoter of the invention, resulting in two fragments excised from the modified alpha promoter (pg. 42 lines 1-6). The specification continues to teach that ~700 bp and 1.7 kb fragments were removed from said alpha promoter, and modified using specific restriction enzymes to result in the isolated nucleic acid molecule of SEQ ID NO: 1 which is 5735 bp in size, and named $MHCmin^{TetO}$ (pg. 42 parags. 2-3). The specification continues to teach that an expression vector comprising the ELC1a gene driven by the $MHCmin^{TetO}$ (SEQ ID NO: 1) promoter was injected into single cell embryos of FVB/N mice, and the injected embryos implanted into pseudopregnant CBA/B6 foster mothers (pg. 44 lines 1-5). The specification continues to teach that transgenic mice comprising $MHCmin^{TetO}$- ELC1a had ELC1a gene expression in the ventricles of the heart (pg. 44 last two parags. bridge pg. 45 parags. 1-3). Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only characteristic described is that the nucleic acid is capable of initiating transcription in cardiac tissue. However, this cannot be used as an identifying characteristics since all species of the claimed genus will have this characteristic. The specification does not teach any other identifying characteristic.

Applicants' attention is directed to the decision in In re Shokal, 113, USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim, In re Soll, 25 C.C.P.A. (Patents) 1309, 97, F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such a number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as halogens, consisting of four species, a reduction in practice of three, or perhaps even two, might server to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a nucleotide sequence having at least 95% identity to the sequence set forth in SEQ ID NO:1, wherein said nucleotide sequence is capable of initiating transcription in cardiac tissue, at the time that application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

No Claims are Allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 1-571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Montanari, Ph.D

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER